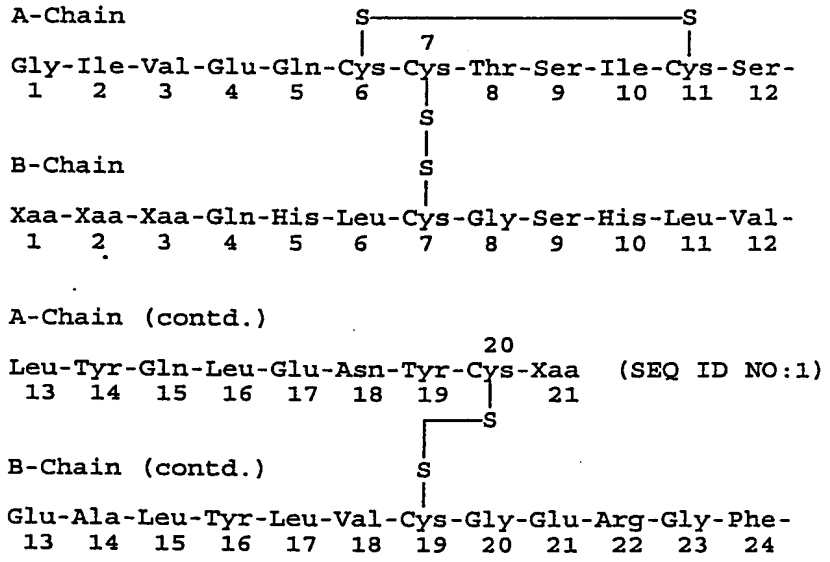
CLAIMS

What is claimed is:

1. A pharmaceutical composition for the treatment of diabetes in a patient in need of such treatment, comprising a sodium phosphate buffer and a therapeutically effective amount of a derivative of a parent insulin having the following sequence:



B-Chain (contd.)

Phe-Xaa-Xaa-Xaa-Xaa-Xaa (SEQ ID NO:2)
25 26 27 28 29 30

wherein

Xaa at position A21 is any codable amino acid except Lys, Arg and Cys;

Xaa at positions B1, B2, B3, B26, B27, B28, B29 and B30 are, independent of each other, any codable amino acid except Cys or deleted; and a lipophilic group W is attached to the amino group of the N-terminal amino acid of the B-chain in which the lipophilic group W has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged or a lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid of the B-chain in which the lipophilic group Z has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged, provided that

(a) when B1-B2-B3 is Phe-Val-Asn and A21 is Asn and B26-B27-B28-B29-B30 is Tyr-Thr-Pro-Lys-Thr or Tyr-Thr-Pro-Lys-Ala, then the lipophilic group W or Z always contains a group which can be negatively charged; and

(b) when B29 and B30 are deleted and the lipophilic group Z is present and B1, B2 and B3 are not deleted then B1-B2 is different from Phe-Val or B26-B27-B28 is different from Tyr-Thr-Pro or both B1-B2 and B26-B27-B28 are different from said sequences; and

(c) when B29 and B30 are deleted and the lipophilic group Z is present and one of B1, B2 or B3 is deleted then the N-terminal amino acid of the B-chain is different from Val or the sequence B26-B27-B28 is different from Tyr-Thr-Pro or both the N-terminal amino acid of the B-chain and the sequence B26-B27-B28 are different from Val and Tyr-Thr-Pro respectively.

2. The pharmaceutical composition of claim 1, wherein Xaa at position A21 is an amino acid selected from the group comprising Ala, Asn, Gln, Glu, Gly and Ser.

3. The pharmaceutical composition of claim 1, wherein Xaa at position B1 is Phe or is deleted.

4. The pharmaceutical composition of claim 1, wherein Xaa at position B2 is Ala or Val.

5. The pharmaceutical composition of claim 1, wherein Xaa at position B3 is an amino acid selected from the group comprising Asn, Gln, Glu, and Thr.

6. The pharmaceutical composition of claim 1, wherein Xaa at position B26 is Tyr.

7. The pharmaceutical composition of claim 1, wherein Xaa at position B27 is Thr.

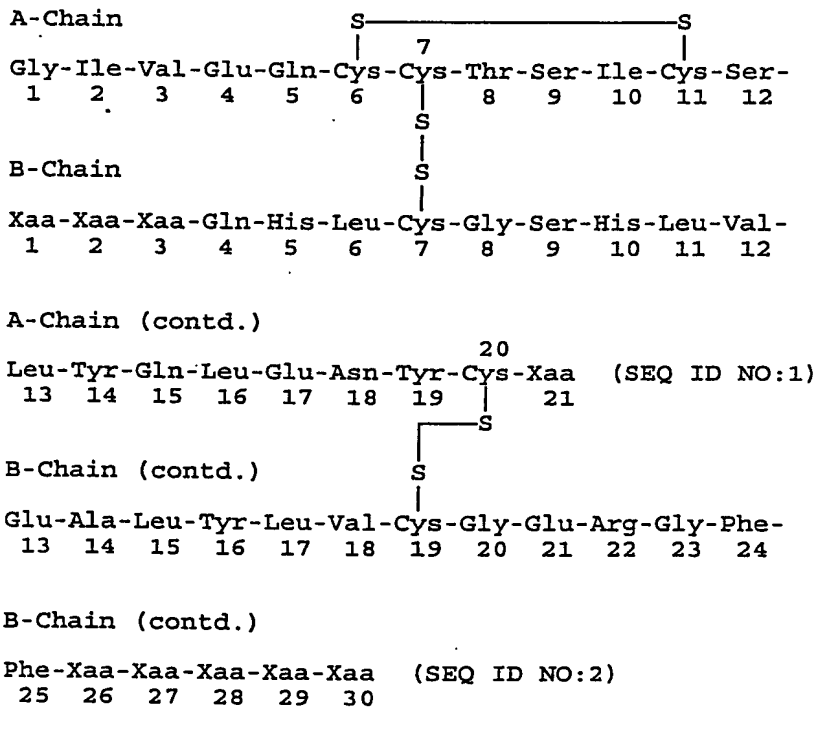
8. The pharmaceutical composition of claim 1, wherein the lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid via an amide bond.

9. The pharmaceutical composition of claim 1, wherein the parent insulin is des(B28-B30) human insulin.

10. The pharmaceutical composition of claim 9, further comprising an insulin analogue which has a rapid onset of action.

11. A method of treating diabetes in a patient in need of such a treatment, comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 1.

12. A pharmaceutical composition for the treatment of diabetes in a patient in need of such treatment, comprising a therapeutically effective amount of a hexameric complex which contains a derivative of a parent insulin having the following sequence:



wherein

Xaa at position A21 is any codable amino acid except Lys, Arg and Cys;

Xaa at positions B1, B2, B3, B26, B27, B28, B29 and B30 are, independent of each other, any codable amino acid except Cys or deleted; and a lipophilic group W is attached to the amino group of the N-terminal amino acid of the B-chain in which the lipophilic group W has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged or a lipophilic group Z is attached to the carboxyl group of the C-terminal amino

acid of the B-chain in which the lipophilic group Z has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged, provided that

(a) when B1-B2-B3 is Phe-Val-Asn and A21 is Asn and B26-B27-B28-B29-B30 is Tyr-Thr-Pro-Lys-Thr or Tyr-Thr-Pro-Lys-Ala, then the lipophilic group W or Z always contains a group which can be negatively charged; and

(b) when B29 and B30 are deleted and the lipophilic group Z is present and B1, B2 and B3 are not deleted then B1-B2 is different from Phe-Val or B26-B27-B28 is different from Tyr-Thr-Pro or both B1-B2 and B26-B27-B28 are different from said sequences; and

(c) when B29 and B30 are deleted and the lipophilic group Z is present and one of B1, B2 or B3 is deleted then the N-terminal amino acid of the B-chain is different from Val or the sequence B26-B27-B28 is different from Tyr-Thr-Pro or both the N-terminal amino acid of the B-chain and the sequence B26-B27-B28 are different from Val and Tyr-Thr-Pro respectively. .

13. The pharmaceutical composition of claim 12, wherein the hexameric complex is a hexamer of the derivative.

14. The pharmaceutical composition of claim 12, wherein the hexameric complex comprises two or more zinc ions and three or more molecules of a phenolic compound.

15. The pharmaceutical composition of claim 14, wherein the hexameric complex comprises three or more molecules of a mixture of phenol and m-cresol.

16. The pharmaceutical composition of claim 12, wherein Xaa at position A21 is an amino acid selected from the group comprising Ala, Asn, Gln, Glu, Gly and Ser.

17. The pharmaceutical composition of claim 12, wherein Xaa at position B1 is Phe or is deleted.

18. The pharmaceutical composition of claim 12, wherein Xaa at position B2 is Ala or Val.

19. The pharmaceutical composition of claim 12, wherein Xaa at position B3 is an amino acid selected from the group comprising Asn, Gln, Glu, and Thr.

20. The pharmaceutical composition of claim 12, wherein Xaa at position B26 is Tyr.

21. The pharmaceutical composition of claim 12, wherein Xaa at position B27 is Thr.

22. The pharmaceutical composition of claim 12, wherein the lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid via an amide bond.

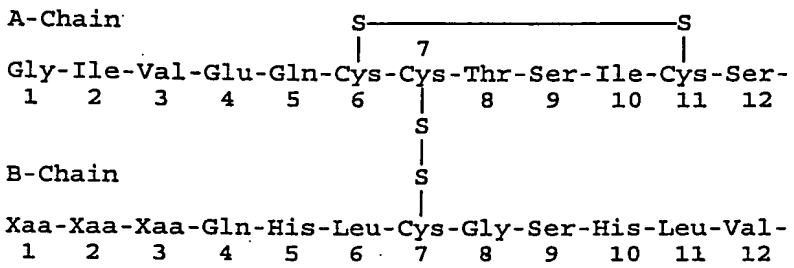
23. The pharmaceutical composition of claim 12, wherein the parent insulin is des(B28-B30) human insulin.

24. The pharmaceutical composition of claim 12, further comprising an insulin analogue which has a rapid onset of action.

25. The pharmaceutical composition of claim 12, which comprises mixed hexamer complexes which are a mixture of an insulin having a protracted profile of action and an insulin having a rapid onset of action, wherein the ratio between the two different insulins in the hexamers being from 1:5 to 5:1.

26. A method of treating diabetes in a patient in need of such a treatment, comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 12.

27. A derivative of a parent insulin having the following sequence:



A-Chain (contd.)

```
                                    20
Leu-Tyr-Gln-Leu-Glu-Asn-Tyr-Cys-Xaa   (SEQ ID NO:1)
 13  14  15  16  17  18  19  |   21
                             |
                             S
                             |
B-Chain (contd.)             S
                             |
Glu-Ala-Leu-Tyr-Leu-Val-Cys-Gly-Glu-Arg-Gly-Phe-
 13  14  15  16  17  18  19  20  21  22  23  24
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B-Chain (contd.)

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Phe-Xaa-Xaa-Xaa-Xaa-Xaa   (SEQ ID NO:2)
 25  26  27  28  29  30
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wherein

Xaa at position A21 is any codable amino acid except Lys, Arg and Cys;

Xaa at positions B1, B2, B3 and B29 are independently any codable amino acid except Cys or deleted;

Xaa at positions B26 and B27 are independently any codable amino acid except Cys;

Xaa at position B30 is any codable amino acid except Cys, a dipeptide which does not contain Cys or Arg, a tripeptide which does not contain Cys or Arg, a tetrapeptide which does not contain Cys or Arg, or deleted; wherein (a) a lipophilic group W is attached to the amino group of the N-terminal amino acid of the B-chain in which the lipophilic group W has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged or (b) a lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid of the B-chain in which the lipophilic group Z has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged.

28. The derivative of claim 27, wherein the lipophilic group W is attached to the amino group of the N-terminal amino acid in the B-chain.

29. The derivative of claim 27, wherein the lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid in the B-chain.

30. The derivative of claim 27, wherein Xaa at position A21 is an amino acid selected from the group comprising Ala, Asn, Gln, Glu, Gly and Ser.

31. The derivative of claim 27, wherein Xaa at position B1 is Phe or is deleted.

32. The derivative of claim 27, wherein Xaa at position B2 is Ala or Val.

33. The derivative of claim 27, wherein Xaa at position B3 is an amino acid selected from the group comprising Asn, Gln, Glu, and Thr.

34. The derivative of claim 27, wherein Xaa at position B26 is Tyr.

35. The derivative of claim 27, wherein Xaa at position B27 is Thr.

36. The derivative of claim 27, wherein Xaa at position B29 is Lys or Thr.

37. The derivative of claim 27, wherein Xaa at position B30 is Thr or ϵ-acylated Lys.

38. The derivative of claim 27, wherein Xaa at position B30 is deleted.

39. The derivative of claim 28, wherein the lipophilic group W is attached to the amino group of the N-terminal amino acid via an amide bond.

40. The derivative of claim 39, wherein the lipophilic group W is $CH_3(CH_2)_nCH(COOH)NH\text{-}CO(CH_2)_2CO$- and n is an integer from 9 to 15.

41. The derivative of claim 29, wherein the lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid via an amide bond.

42. The derivative of claim 41, wherein the lipophilic group Z is $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_mCH_3$ and m is an integer from 8 to 18.

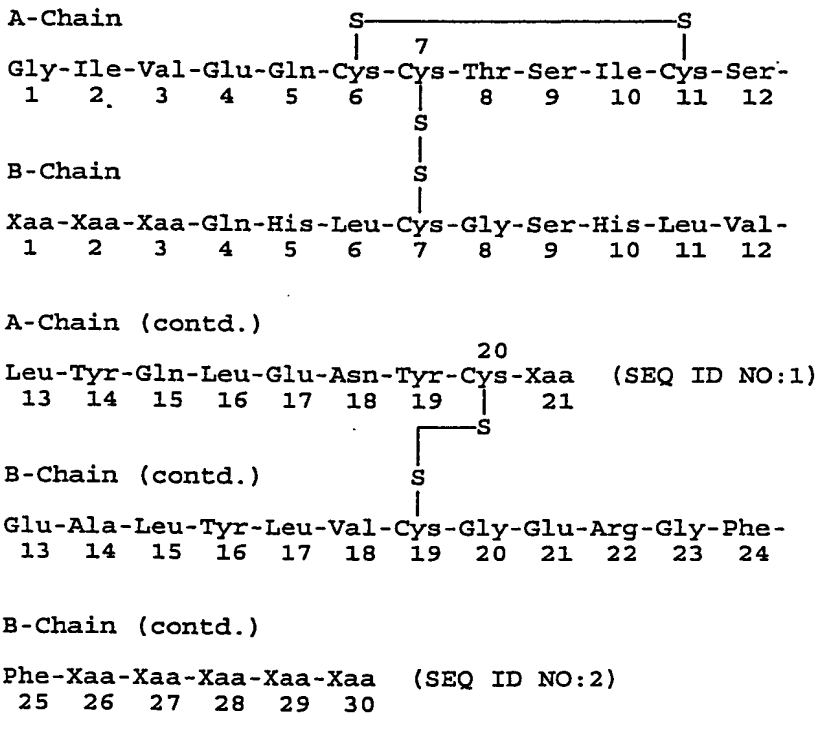
43. An derivative of claim 27, wherein the C-terminal amino acid of the B-chain is ϵ-acylated Lys and the amino acid next to the C-terminal amino acid is Gly.

44. A pharmaceutical composition comprising a therapeutically effective amount of the derivative of claim 27 together with a pharmaceutically acceptable carrier.

45. The pharmaceutical composition of claim 44, further comprising an insulin or an insulin analogue which has a rapid onset of action.

46. A method of treating diabetes in a patient in need of such a treatment, comprising administering to the patient a pharmaceutical composition of claim 44.

47. A derivative of a parent insulin having the following sequence:



wherein

Xaa at position A21 is any codable amino acid except Lys, Arg and Cys;

Xaa at positions B1, B2 and B3 are independently any codable amino acid except Cys or deleted;

Xaa at positions B26, B27, B28 and B29 are independently any codable amino acid except Cys;

Xaa at position B30 is a dipeptide which does not contain Cys or Arg, a tripeptide which does not contain Cys or Arg, or a tetrapeptide which does not contain Cys or Arg; and (a) a lipophilic group W is attached to the amino group of the N-terminal amino acid of the B-chain in which the lipophilic group W has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged or (b) a lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid of the B-chain in which the lipophilic group Z has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged.

48. The derivative of claim 47, wherein the lipophilic group W is attached to the amino group of the N-terminal amino acid in the B-chain.

49. The derivative of claim 47, wherein the lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid in the B-chain.

50. The derivative of claim 47, wherein Xaa at position A21 is an amino acid selected from the group comprising Ala, Asn, Gln, Glu, Gly and Ser.

51. The derivative of claim 47, wherein Xaa at position B1 is Phe or is deleted.

52. The derivative of claim 47, wherein Xaa at position B2 is Ala or Val.

53. The derivative of claim 47, wherein Xaa at position B3 is an amino acid selected from the group comprising Asn, Gln, Glu, and Thr.

54. The derivative of claim 47, wherein Xaa at position B26 is Tyr.

55. The derivative of claim 47, wherein Xaa at position B27 is Thr.

56. The derivative of claim 47, wherein Xaa at position B28 is Pro.

57. The derivative of claim 47, wherein Xaa at position B29 is Lys or Thr.

58. The derivative of claim 47, wherein Xaa at position B28 is Lys and Xaa at position B29 is Pro.

59. The derivative of claim 47, wherein Xaa at position B28 is Pro and Xaa at position B29 is Thr.

60. The derivative of claim 48, wherein the lipophilic group W is attached to the amino group of the N-terminal amino acid via an amide bond.

61. The derivative of claim 60, wherein the lipophilic group W is $CH_3(CH_2)_nCH(COOH)NH\text{-}CO(CH_2)_2CO$- and n is an integer from 9 to 15.

62. The derivative of claim 49, wherein the lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid via an amide bond.

63. The derivative of claim 62, wherein the lipophilic group Z is $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_mCH_3$ and m is an integer from 8 to 18.

64. The derivative of claim 63, wherein the parent insulin is Thr^{B29} human insulin.

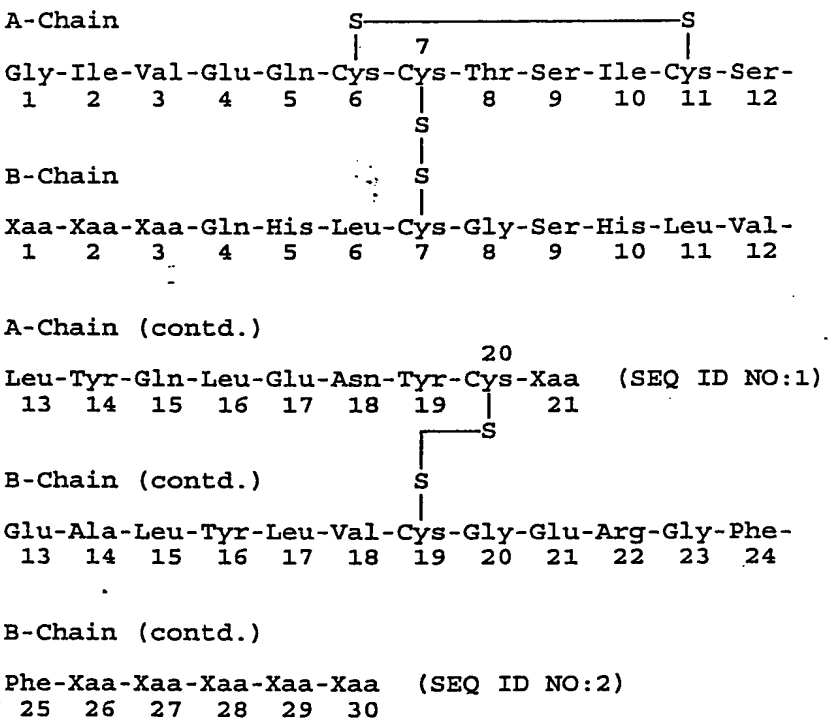
65. The derivative of claim 47, wherein the C-terminal amino acid of the B-chain is ϵ-acylated Lys and the amino acid next to the C-terminal amino acid is Gly.

66. A pharmaceutical composition comprising a therapeutically effective amount of the derivative of claim 47 together with a pharmaceutically acceptable carrier.

67. The pharmaceutical composition of claim 66, further comprising an insulin or an insulin analogue which has a rapid onset of action.

68. A method of treating diabetes in a patient in need of such a treatment, comprising administering to the patient a pharmaceutical composition of claim 66.

69. A derivative of a parent insulin having the following sequence:



wherein at least one amino acid or sequence of amino acids selected from the group comprising B1, B30, B(29-30), B(28-30), B(27-30) and B(26-30) is deleted and

Xaa at position A21 is any codable amino acid except Lys, Arg and Cys;

Xaa at positions B1, B2, B3, B26, B27, B28 and B29 are independently any codable amino acid except Cys or deleted;

Xaa at position B30 is any codable amino acid except Cys, a dipeptide which dos not contain Cys or Arg, a tripeptide which does not contain Cys or Arg, a tetrapeptide which does not contain Cys or Arg, or deleted; and (a) a lipophilic group W is attached to the amino group of the N-terminal amino acid of the B-chain in which the lipophilic group W has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged or (b) a lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid of the B-chain in which the lipophilic group Z has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged, provided that

(a) when B29 and B30 are deleted and a group Z as defined above is present at the C-terminal amino acid of the B-chain and neither B1, B2 nor B3 is deleted then B1-B2 is

different from Phe-Val or B26-B27-B28 is different from Tyr-Thr-Pro or both B1-B2 and B26-B27-B28 are different from said sequences; and

(b) when B29 and B30 are deleted and a group Z as defined above is present at the C-terminal amino acid of the B-chain and one of B1, B2 or B3 is deleted then the N-terminal amino acid of the B-chain is different from Val or the sequence B26-B27-B28 is different from Tyr-Thr-Pro or both the N-terminal amino acid of the B-chain and the sequence B26-B27-B28 are different from Val and Tyr-Thr-Pro respectively.

70. The derivative of claim 69, wherein the lipophilic group W is attached to the amino group of the N-terminal amino acid in the B-chain.

71. The derivative of claim 69, wherein the lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid in the B-chain.

72. The derivative of claim 69, wherein Xaa at position A21 is an amino acid selected from the group comprising Ala, Asn, Gln, Glu, Gly and Ser.

73. The derivative of claim 69, wherein Xaa at position B1 is Phe or is deleted.

74. The derivative of claim 69, wherein Xaa at position B2 is Ala or Val.

75. The derivative of claim 69, wherein Xaa at position B3 is an amino acid selected from the group comprising Asn, Gln, Glu, and Thr.

76. The derivative of claim 69, wherein Xaa at position B26 is Tyr.

77. The derivative of claim 69, wherein Xaa at position B27 is Thr.

78. The derivative of claim 69, wherein Xaa at position B28 is Pro.

79. The derivative of claim 69, wherein Xaa at position B29 is Lys or Thr.

80. The derivative of claim 69, wherein Xaa at position B30 is Thr or ϵ-acylated Lys.

81. The derivative of claim 69, wherein Xaa at position B30 is deleted.

82. The derivative of claim 69, wherein Xaa at position B28 is Lys and Xaa at position B29 is Pro.

83. The derivative of claim 69, wherein Xaa at position B28 is Pro and Xaa at position B29 is Thr.

84. The derivative of claim 70, wherein the lipophilic group W is attached to the amino group of the N-terminal amino acid via an amide bond.

85. The derivative of claim 84, wherein the lipophilic group W is $CH_3(CH_2)_nCH(COOH)NH\text{-}CO(CH_2)_2CO$- and n is an integer from 9 to 15.

86. The derivative of claim 71, wherein the lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid via an amide bond.

87. The derivative of claim 86, wherein Z is $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_mCH_3$ and m is an integer from 8 to 18.

88. The derivative of claim 87, wherein the parent insulin is des(B28-B30) human insulin.

89. The derivative of claim 87, wherein the parent insulin is des(B27-B30) human insulin.

90. The derivative of claim 87, wherein the parent insulin is attached is des(B26-B30) human insulin.

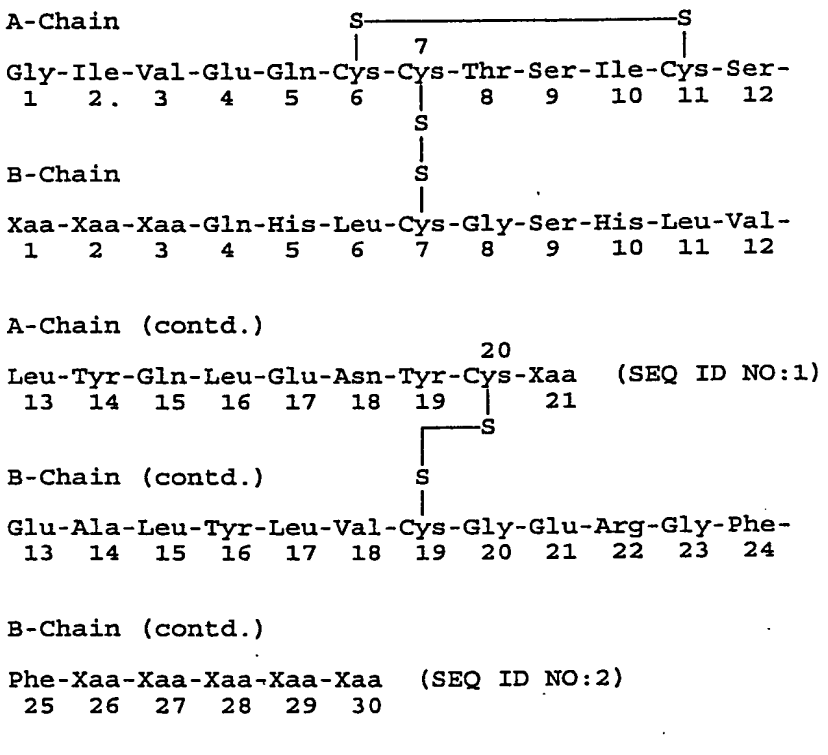
91. The derivative of claim 69, wherein the C-terminal amino acid of the B-chain is ϵ-acylated Lys and the amino acid next to the C-terminal amino acid is Gly.

92. A pharmaceutical composition, comprising a therapeutically effective amount of the derivative of claim 69 together with a pharmaceutically acceptable carrier.

93. The pharmaceutical composition of claim 92, further comprising an insulin or an insulin analogue which has a rapid onset of action.

94. A method of treating diabetes in a patient in need of such a treatment, comprising administering to the patient a pharmaceutical composition of claim 92.

95. A derivative of a parent insulin having the following sequence:



wherein

Xaa at position A21 is any codable amino acid except Lys, Arg and Cys;

Xaa at positions B1, B2 and B3 are independently any codable amino acid except Cys or deleted;

Xaa at positions B26, B27 and B28 are independently any codable amino acid except Cys;

Xaa at position B30 is any codable amino acid except Cys, a dipeptide which does not contain Cys or Arg, a tripeptide which does not contain Cys or Arg, a tetrapeptide which does not contain Cys or Arg, or deleted; and (a) a lipophilic group W is attached to the amino group of the N-terminal amino acid of the B-chain in which the lipophilic group W has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged or (b) a lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid of the B-chain in which the lipophilic group Z has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged.

96. The derivative of claim 95, wherein the lipophilic group W is attached to the amino group of the N-terminal amino acid in the B-chain.

97. The derivative of claim 95, wherein the lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid in the B-chain.

98. The derivative of claim 95, wherein Xaa at position A21 is an amino acid selected from the group comprising Ala, Asn, Gln, Glu, Gly and Ser.

99. The derivative of claim 95, wherein Xaa at position B1 is Phe or is deleted.

100. The derivative of claim 95, wherein Xaa at position B2 is Ala or Val.

101. The derivative of claim 95, wherein Xaa at position B3 is an amino acid selected from the group comprising Asn, Gln, Glu, and Thr.

102. The derivative of claim 95, wherein Xaa at position B26 is Tyr.

103. The derivative of claim 95, wherein Xaa at position B27 is Thr.

104. The derivative of claim 95, wherein Xaa at position B28 is Pro.

105. The derivative of claim 95, wherein Xaa at position B30 is Thr or ϵ-acylated Lys.

106. The derivative of claim 95, wherein Xaa at position B30 is deleted.

107. The derivative of claim 95, wherein Xaa at position B28 is Pro and Xaa at position B29 is Thr.

108. The derivative of claim 96, wherein the lipophilic group W is attached to the amino group of the N-terminal amino acid via an amide bond.

109. The derivative of claim 108, wherein the lipophilic group W is $CH_3(CH_2)_nCH(COOH)NH\text{-}CO(CH_2)_2CO$- and n is an integer from 9 to 15.

110. The derivative of claim 97, wherein the lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid via an amide bond.

111. The derivative of claim 110, wherein the lipophilic group Z is $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_mCH_3$ and m is an integer from 8 to 18.

112. The derivative of claim 111, wherein the parent insulin is Thr^{B29} human insulin.

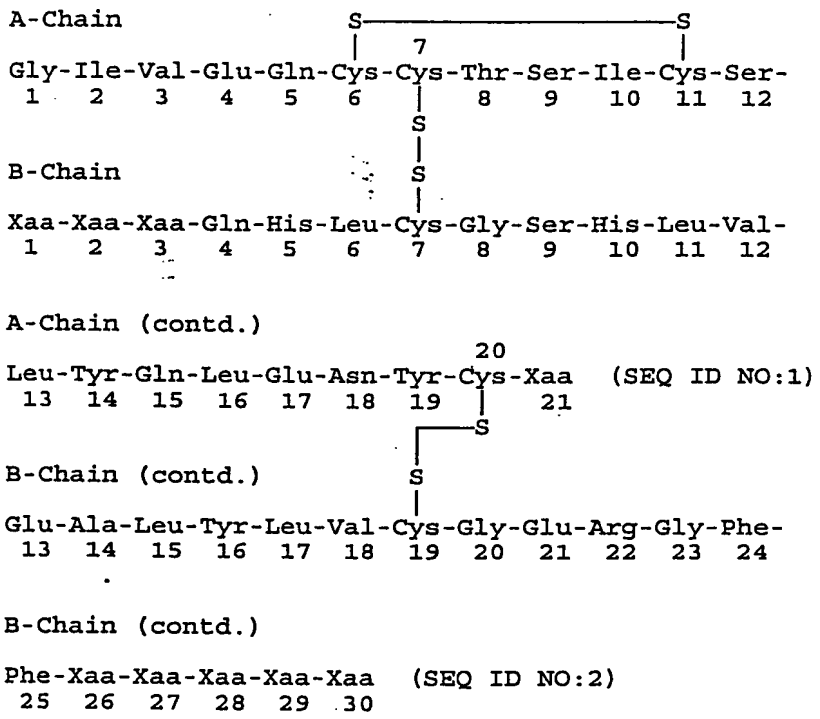
113. The derivative of claim 95, wherein the C-terminal amino acid of the B-chain is ϵ-acylated Lys and the amino acid next to the C-terminal amino acid is Gly.

114. A pharmaceutical composition for the treatment of diabetes in a patient in need of such treatment, comprising a therapeutically effective amount of the derivative of claim 95 together with a pharmaceutically acceptable carrier.

115. The pharmaceutical composition of claim 114, further comprising an insulin or an insulin analogue which has a rapid onset of action.

116. A method of treating diabetes in a patient in need of such a treatment, comprising administering to the patient the pharmaceutical composition of claim 114.

117. A derivative of a parent insulin having the following sequence:



wherein

Xaa at position A21 is any codable amino acid except Lys, Arg and Cys;

Xaa at positions B1, B2 and B3 are independently any codable amino acid except Cys or deleted;

Xaa at positions B26, B27, B28 and B29 are independently any codable amino acid except Cys;

Xaa at position B30 is Lys; and (a) a lipophilic group W is attached to the amino group of the N-terminal amino acid of the B-chain in which the lipophilic group W has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged or (b) a lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid of the B-chain in which the lipophilic group Z has from 12 to 40 carbon atoms and optionally contains a group which can be negatively charged.

118. The derivative of claim 117, wherein the lipophilic group W is attached to the amino group of the N-terminal amino acid in the B-chain.

119. The derivative of claim 117, wherein the lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid in the B-chain.

120. The derivative of claim 117, wherein Xaa at position A21 is an amino acid selected from the group comprising Ala, Asn, Gln, Glu, Gly and Ser.

121. The derivative of claim 117, wherein Xaa at position B1 is Phe or is deleted.

122. The derivative of claim 117, wherein Xaa at position B2 is Ala or Val.

123. The derivative of claim 117, wherein Xaa at position B3 is an amino acid selected from the group comprising Asn, Gln, Glu, and Thr.

124. The derivative of claim 117, wherein Xaa at position B26 is Tyr.

125. The derivative of claim 117, wherein Xaa at position B27 is Thr.

126. The derivative of claim 117, wherein Xaa at position B28 is Pro.

127. The derivative of claim 117, wherein Xaa at position B29 is Lys or Thr.

128. The derivative of claim 117, wherein Xaa at position B28 is Lys and Xaa at position B29 is Pro.

129. The derivative of claim 117, wherein Xaa at position B28 is Pro and Xaa at position B29 is Thr.

130. The derivative of claim 118, wherein the lipophilic group W is attached to the amino group of the N-terminal amino acid via an amide bond.

131. The derivative of claim 130, wherein the lipophilic group W is $CH_3(CH_2)_nCH(COOH)NH\text{-}CO(CH_2)_2CO$- and n is an integer from 9 to 15.

132. The derivative of claim 119, wherein the lipophilic group Z is attached to the carboxyl group of the C-terminal amino acid via an amide bond.

133. The derivative of claim 117, wherein the C-terminal amino acid of the B-chain is ϵ-acylated Lys and the amino acid next to the C-terminal amino acid is Gly.

134. A pharmaceutical composition, comprising a therapeutically effective amount of the derivative of claim 117 together with a pharmaceutically acceptable carrier.

135. The pharmaceutical composition of claim 134, further comprising an insulin or an insulin analogue which has a rapid onset of action.

136. A method of treating diabetes in a patient in need of such a treatment, comprising administering to the patient the pharmaceutical composition of claim 134.